REMARKS

In the application, Claims 1- 24 are pending and rejected. In view of the Examiner's comments, the claims have been amended as set forth above. Applicants now request reconsideration of the application as amended.

Withdrawn Objections/Rejections

The Examiner has withdrawn his objection to Claim 23 based on a formality. The Examiner has also withdrawn the objections to Claims 1-20 and 23 under 35 U.S.C. 112, second paragraph. Finally, the Examiner has withdrawn all prior art rejections in view of the amendments filed on October 10, 2008.

35 U.S.C. § 101

The Examiner has rejected Claims 1-24 under 35 U.S.C. § 101 as being directed to non-statutory subject matter.

In the Examiner's comments in response to Applicants' comments, he states that no gene expression is required, and that the output "corresponds" to gene expression. Since the intended end result of each claim is to effect gene expression, the claims have been amended to change "corresponds" to "comprises" or "produces". Furthermore, references to "genetic computing" are removed from the claims to avoid the appearance that the claimed invention is simply a computing mechanism using genes. The invention provides a method for customizing gene expression to produce genetic responses that otherwise would not occur.

In view of the claim amendments, it is submitted that a physical transformation occurs as a result of the claimed steps, and that, therefore, the claims are directed to statutory subject matter. The Examiner is respectfully requested to withdraw the rejection under § 101.

35 U.S.C. §103

The Examiner has rejected Claim 21 under 35 U.S.C. §103 as being unpatentable over Bujard et al. (U.S. Patent 5,814,618) in view of Wasiewicz et al. (Cybernetics and Systems: An International Journal, volume 31, 2000, pages 283-315).

The Examiner asserts that Bujard et al. teaches the combination of two distinct polypeptides to implement an AND function to regulate gene expression by controlling the level of expression.

Applicants again respectfully submit that Bujard et al. describe regulation of gene expression that involves only a single chimeric protein that mixes different interaction domains together with the DNA binding domain of a specific regulator (TetR). In other words, Bujard, et al. teach only a single regulator. For purposes of illustration, call this regulator "A". In logic, (A AND A) will always be A; (A OR A) will always be A. Bujard et al. cannot possibly suggest a logic function that requires two or more inputs, each of which is a *different regulatory protein*. In Bujard et al., there is no requirement that two different conditions be present in a certain combination in order to produce a conditional result that is different for each logic function. Accordingly, Bujard et al. does not teach or suggest a logic function that operates on two or more different regulatory proteins to produce an output that is a unique gene expression, as claimed.

Claim 21 has been amended to specify that there are two or more inputs and that each input is a different regulatory protein. Further, the gene expression resulting from each logic function is specified as different. Neither of these limitations is taught or suggested by Bujard et al.

The Examiner relies on Wasiewicz et al. for their teaching of a molecular computer and asserts that it would be obvious to modify the teachings of Bujard et al. with that of Wasiewicz et al. to arrive at the claimed gene computing method. Applicants respectfully disagree.

First, Bujard et al. does not teach or suggest a logic function. Using a specific combination of two polypeptides to form a single functional protein is addition, not a logical AND operation. The absence of the teaching of a logical operation by Bujard et al. would result in there being no basis for making a mental connection to the molecular computing taught by Wasiewicz et al.

Second, Bujard et al. describe modification of gene expression in a cell, i.e., *in vivo*. Wasiewicz et al. describe the use of different DNA sequences *in vitro* to symbolize rules in a knowledge tree. Nothing in Wasiewicz et al. suggests regulation of gene expression in a cell, or any possible *in vivo* application; DNA is simply a symbol, a string of letters, that can be used to

represent different rules depending on the sequence of bases. Computation using the molecular computer of Wasiewicz et al. requires laboratory processing to synthesize the DNA sequences, including annealing, ligation, and electrophoresis. There is no suggestion that these DNA sequences (inference paths) can be used as anything but unique strings of bases that correspond to rules and are capable of replicating. There is no suggestion of regulation of gene expression in a cell by the DNA sequences used in this molecular computer, and the only mention of an *in vivo* operation is the potential use of bacteria to multiply the inference paths. The only common ground between Bujard et al. and Wasiewicz is that DNA is somehow manipulated in both. In fact, these two references are so unrelated that there could be no reasonable connection made by one of skill in the art that would lead them to combine the references to render obvious Applicants' invention related to a method for programming gene expression in a cell by implementing different logic functions on different inputs, each of which are regulatory proteins.

An important object of the present invention is to produce engineered promoters in cells by combining multiple different "cues" to program a genetic response. For example, one can program the regulatory sequences to turn on a reporter gene only if the pattern of regulatory protein activities (from two or more regulatory proteins) in a cell matches one of those unique to tumor cells. The reporter gene can then serve as the indicator of tumor cells and guide external treatment such as radiation or surgery.

The key to the invention is that the regulatory proteins are used combinatorially -- a combination of conditions must occur, i.e., regulators must be present, in order to obtain the desired gene expression. For example, by inserting a designed regulatory region controlling a reporter gene (e.g., the green fluorescence protein or GFP) into a population of bacteria equipped with a number of special chemical detectors, one can program these bacteria to look for and report unique patterns of detected traits that correspond to specific chemical pollutants or biological warfare agents in the environment. Alternatively, the reporter gene may be replaced by a therapeutic gene to target the conditions under which the regulatory proteins were produced, e.g., detection of proteins from tumor cells would trigger expression of genes to induce apoptosis. The use of multiple cues (different inputs) as opposed to a single cue, as taught by Bujard et al., makes discrimination possible, an essential component for successful gene therapy. The inventive method does much more that just increase the level of an otherwise expected expression as taught by Bujard

et al.; it promotes "designer gene expression" that would not occur under normal conditions but for the programming that is done by way of adjustments to the cis-regulatory region, as claimed.

Accordingly, it is respectfully submitted that the combination of Bujard et al. with Wasiewicz et al. fails to teach or suggest Applicants' invention as now claimed. The Examiner is requested to withdraw the §103 rejection of claim 21 over the cited combination.

The Examiner has rejected Claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. as applied to Claim 21 above, in further view of Kirch et al. (*Oncogene*, 1999, volume 18, pages 2728-2738) in view of Orkin (*Cell*, volume 63, 1990, pages 665-672).

Kirch et al. is cited for its disclosure of synergistic activation of transcription and selective mutation of the sequence to reduce or eliminate transcription. Orkin is cited for its discussion of transcription at locus controlled regions that result in long distance interactions.

As discussed above, the combination of Bujard et al. with Wasiewicz et al. fails to teach or suggest a method for controlling gene expression by taking two or more different inputs, where each input comprises a regulatory protein, and performing a logic operation on the inputs to produce an output that is a desired gene expression in a cell, and where the logic operation is effected by adjusting DNA binding strength and locating to select the types of interactions between the regulatory proteins and the interactive binding at the binding sites.

While Kirch et al. may teach an AND-like function as a result of the use of a combination of different motifs, it provides nothing to suggest that the same regulators can be combined by a different designer promoter, created by varying binding strengths and locations in cis-regulatory regions, to implement other logic functions, such as OR, NAND, or XOR, to drive a different gene expression in the same cell. Accordingly, Kirch et al. does not bring to a combination with Bujard et al. and Wasiewicz et al. what is missing from that combination. As such, the combination of the three references does not teach or suggest Applicants' invention as now claimed.

While Orkin may teach protein-protein interactions in regulating transcription control, it does not teach or suggest a plurality of different logic functions that can be implemented by various combinations of the two or more different regulatory proteins and adjustment of binding strengths and locations in cis-regulatory regions as claimed in the amended claims to produce a different

genetic response in the cell. Because both Kirch et al. and Orkin fail to teach or suggest what is missing from the combination of Bujard et al. and Wasiewicz et al., the combination of the four references would not render Applicants' invention obvious to one of skill in the art. Accordingly, the combination of Bujard et al., Wasiewicz et al., Kirch et al. and Orkin fails to teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions to produce different gene expression results in a cell as claimed. The Examiner is respectfully requested to withdraw the rejection under §103.

The Examiner has rejected Claims 2 and 12 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin as applied to Claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 and 21 above, and further in view of Kirchhamer et al. (*PNAS*, volume 93, 1996, pages 9322-9328).

Kirchhamer et al. are cited for their disclosure of modular cis-regulatory organization, however, Kirchhamer et al. do not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions on two or more different inputs, each comprising a regulatory protein, to effect a different gene expression for each logic function as claimed. As a result, combination of the teachings of Kirchhamer et al. with that of Bujard et al., Kirch et al. and Orkin does not render the claimed methods obvious.

The Examiner has rejected Claims 4, 6, 14, and 16 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin as applied to Claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 and 21 above, and further in view of Renkawitz (*Trends in Genetics*, 1990, volume 6, pages 192-197).

The Renkawitz article is cited for its disclosure of transcription repression, however, Renkawitz does not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions on two or more different inputs, each comprising a regulatory protein, to effect a different gene expression for each logic function as claimed. As a result, combination of the teachings of Renkawitz with that of Bujard et al., Wasiewicz et al., Kirch et al. and Orkin does not render the claimed methods obvious.

The Examiner has rejected Claims 9 and 19 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin as applied to Claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 and 21 above, and further in view of Ogawa (U.S. Patent 5,535,382 issued July 9, 1996).

Ogawa is cited for its disclosure of the use of logic functions in minimal conjunctive normal form for ranking the results of a document retrieval system. It is respectfully submitted that, Ogawa not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions on two or more different inputs, each comprising a regulatory protein, to effect a different gene expression for each logic function as claimed.. Furthermore, as there is nothing in either Bujard et al., Wasiewicz et al., Kirch et al. and Orkin, alone or in combination, that provides any suggestion of attempting to implement a plurality of different logic functions acting on different inputs that are regulatory proteins for controlling transcription to produce a different genetic response for each logic function, there would have been no motivation to combine the teachings of Ogawa relative to a document retrieval system with any of Bujard et al., Wasiewicz et al, Kirch et al. and Orkin.

The Examiner has rejected Claims 10 and 20 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin as applied to Claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 and 21 above, and further in view of Gardner et al. (*Nature*, 2000, volume 403, pages 339-343).

For the reasons set forth in the preceding discussion, the combination of Bujard et al., Wasiewicz et al., Kirch et al. and Orkin with Ogawa does not render the claimed invention obvious, and, therefore, are patentable over the prior art. The combination of the four references with Gardner et al., which teach a genetic switch, still fails to teach or suggest the implementation of a plurality of different logic functions acting on different inputs that are regulatory proteins for controlling transcription to produce a different genetic response for each logic function. A switch is either "on" or "off"; it does not perform logic functions, nor does it teach how to control transcription by combining two or more regulatory proteins with a cis-regulatory region that has adjustable binding strengths and sites to selectively induce different genetic responses in a cell.

While it may ultimately be possible to implement combinatorial control of gene expression by creating a genetic circuit from a series of genetic switches, such an approach would require many operations with intermediate regulators before achieving the ultimate desired genetic response. This is distinguishable from the present invention, which designs cis-regulatory control so that the final gene expression output is derived from one step of the levels of the input regulators without the need for intermediate regulators and gene expression. Accordingly, the teachings of Gardner, et al. would not render Applicants' invention obvious when combined the teachings of Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin.

The Examiner has rejected Claim 22 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al., as applied to Claim 21 above, and further in view of Kirchhamer et al.

For the reasons previously stated, the combination of Bujard et al. in view of Wasiewicz et al. fails to teach or suggest Applicants' invention as now claimed.

Kirchhamer et al. are cited for their disclosure of modular cis-regulatory organization, however, Kirchhamer et al. do not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions acting on different inputs that are regulatory proteins for controlling transcription to produce a different genetic response for each logic function. As a result, combination of the teachings of Kirchhamer et al. with that of Bujard et al., does not render the claimed methods obvious.

The Examiner has rejected Claims 23-24 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al., as applied to Claim 21 above, and further in view of Orkin.

The Examiner relies on Orkin for its disclosure of protein-protein interactions in regulating transcription control. However, Orkin does not teach or suggest a plurality of different logic functions acting on different inputs that are regulatory proteins for controlling transcription to produce a different genetic response for each logic function.

For the reasons previously stated, the combination of Bujard et al. in view of Wasiewicz et al. fails to teach or suggest Applicants' invention as now claimed. Because Bujard et al. and

Wasiewicz et al. do not disclose a method for combinatorial control of transcription using logic functions with inputs comprising different regulatory proteins and a different output for each logic function, it is respectfully submitted that the invention as claimed would not be obvious to one of skill in the art because none of the secondary references disclose what is missing from Bujard et al. in view of Wasiewicz et al. Accordingly, the Examiner is respectfully requested to withdraw all rejections under §103.

New Claims

New claim 25 is supported in the specification at paragraphs [0045] and [0075] as published. New claim 26 corresponds to original claims 3 and 13. New claim 27 is supported in the specification at paragraph [0088] as published.

Claims 28-31 have been added to recite specific examples of how the inventive method may be applied to produce programmed genetic response in a cell. New claims 28, 29, and 31 are supported in the specification at paragraph [0090] as published. New claim 30 is supported in the specification at paragraph [0089] as published.

Accordingly, no new matter is introduced by the new claims.

Conclusion

It is believed that all grounds for rejection have been addressed and overcome. The Examiner is respectfully requested to reconsider the claims as amended, withdraw the objections and rejections, and issue a notice of allowance of all claims now pending in the application.

Should the Examiner believe that prosecution of this application might be expedited by further discussion of the issues, he is invited to telephone the undersigned attorney for Applicants at the telephone number indicated below.

Respectfully submitted,

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